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=> s (restriction landmark genomic scanning) or rlgs
L1 297 (RESTRICTION LANDMARK GENOMIC SCANNING) OR RLGS

=> s l1 and methylat?
L2 134 L1 AND METHYLAT?

=> s l2 and py<2000
L3 57 L2 AND PY<2000

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L4 ANSWER 1 OF 37 MEDLINE on STN DUPLICATE 1
AN 1999324188 MEDLINE
DN 99324188 PubMed ID: 10393947
TI Analysis of human peripheral blood T cells and single-cell-derived T cell clones uncovers extensive clonal CpG island **methylation** heterogeneity throughout the genome.
AU Zhu X; Deng C; Kuick R; Yung R; Lamb B; Neel J V; Richardson B; Hanash S
CS Department of Pediatrics, University of Michigan Medical Center, Ann Arbor, MI 48109, USA.
NC AG014783 (NIA)
AR42555 (NIAMS)
CA26803 (NCI)
+
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1999 Jul 6)** 96 (14) 8058-63.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199908
ED Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990826
AB **Methylation** of cytosine residues in CpG dinucleotides is generally associated with silencing of gene expression. DNA **methylation**, as a somatic event, has the potential of diversifying gene expression in individual cells of the same lineage. There is little quantitative data available concerning the extent of **methylation** heterogeneity in individual cells across the genome. T cells from the peripheral blood can be grown as single-cell-derived clones and can be analyzed with respect to their DNA **methylation** patterns by **restriction landmark genomic scanning** . The use of the **methylation**-sensitive enzyme NotI to cut and end-label DNA fragments before their separation in two dimensions provides a quantitative assessment of **methylation** at NotI sites that characteristically occur in CpG islands. We have undertaken quantitative analysis of two-dimensional DNA patterns to determine the extent of **methylation** heterogeneity at NotI sites between peripheral blood single-cell-derived T cell clones from the same individual. A total of 1,068 NotI-tagged fragments were analyzed. A subset of 156 fragments

exhibited marked **methylation** heterogeneity at NotI sites between clones. Their average intensity among clones correlated with their intensity in uncultured, whole-blood-derived T cells, indicating that the **methylation** heterogeneity observed in clones was largely attributable to **methylation** heterogeneity between the individual cells from which the clones were derived. We have cloned one fragment that exhibited variable NotI-site **methylation** between clones. This fragment contained a novel CpG island for a gene that we mapped to chromosome 4. The **methylation** status of the NotI site of this fragment correlated with expression of the corresponding gene. Our data suggest extensive diversity in vivo in the **methylation** and expression profiles of individual T cells at multiple unrelated loci across the genome.

L4 ANSWER 2 OF 37 MEDLINE on STN DUPLICATE 2
AN 1999270213 MEDLINE
DN 99270213 PubMed ID: 10340388
TI Restriction landmark genome scanning for aberrant **methylation** in primary refractory and relapsed acute myeloid leukemia; involvement of the WIT-1 gene.
AU Plass C; Yu F; Yu L; Strout M P; El-Rifai W; Elonen E; Knuutila S; Marcucci G; Young D C; Held W A; Bloomfield C D; Caligiuri M A
CS Department of Microbiology and Immunology, Comprehensive Cancer Center, The Ohio State University, Columbus 43210, USA.
NC 1RO1GM58269 (NIGMS)
2RO1CA68612 (NCI)
P30 CA16058 (NCI)
+
SO ONCOGENE, **(1999 May 20)** 18 (20) 3159-65.
Journal code: 8711562. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199906
ED Entered STN: 19990618
Last Updated on STN: 19990618
Entered Medline: 19990608
AB There is substantial evidence to suggest that aberrant DNA **methylation** in the regulatory regions of expressed genes may play a role in hematologic malignancy. In the current report, the **Restriction Landmark Genomic Scanning** (**RLGS**) method was used to detect aberrant DNA **methylation** (M) in acute myeloid leukemia (AML). **RLGS**-M profiles were initially performed using DNA from diagnostic, remission, and relapse samples from a patient with AML. Rp18, one of the eight spots found that was absent in the relapse sample, was cloned. Sequence analysis showed that the spot represented a portion of the WIT-1 gene on human chromosome 11p13. Rp18 was missing in the relapse sample due to a distinct DNA **methylation** pattern of the WIT-1 gene. Twenty-seven AML patients that entered CR after therapy (i.e., chemosensitive) were studied and only 10 (37%) of the diagnostic bone marrow (BM) samples showed **methylation** of WIT-1. However, seven of eight (87.5%) diagnostic BM samples from primary refractory AML (chemosensitive) showed **methylation** of WIT-1. The incidence of WIT-1 **methylation** in primary refractory AML was significantly higher than that noted in chemosensitive AML (P=0.018). Together, these results indicate that **RLGS**-M can be used to find novel epigenetic alterations in human cancer that are undetectable by standard methods. In addition, these results underline the potential importance of WIT-1 **methylation** in chemoresistant AML.

L4 ANSWER 3 OF 37 MEDLINE on STN DUPLICATE 3
AN 1999303556 MEDLINE

DN 99303556 PubMed ID: 10373323
TI A new tool for the rapid cloning of amplified and hypermethylated human DNA sequences from restriction landmark genome scanning gels.
AU Smiraglia D J; Fruhwald M C; Costello J F; McCormick S P; Dai Z; Peltomaki P; O'Dorisio M S; Cavenee W K; Plass C
CS Department of Medical Microbiology and Immunology, The Ohio State University, Columbus, Ohio 43210, USA.. Smiraglia.1@postbox.acs.ohio-state.edu
NC P30CA16058 (NCI)
R21CA80912 (NCI)
T32 CA09338-20 (NCI)
SO GENOMICS, **(1999 Jun 15)** 58 (3) 254-62.
Journal code: 8800135. ISSN: 0888-7543.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199907
ED Entered STN: 19990806
Last Updated on STN: 19990806
Entered Medline: 19990723
AB Restriction landmark genome scanning (**RLGS**) is an effective genome-scanning technique capable of identifying DNA amplification and aberrant DNA **methylation**. Previously published methods for the cloning of human DNA fragments from **RLGS** gels have been successful only for high-copy-number fragments (repetitive elements or DNA amplifications). We present here the first technique capable of efficiently cloning single-copy human DNA fragments ("spots") identified in **RLGS** profiles. This technique takes advantage of a plasmid-based, human genomic DNA, NotI/EcoRV boundary library. The library is arrayed in microtiter plates. When clones from a single plate are pooled and mixed with genomic DNA, the resultant **RLGS** gel is a normal profile with a defined set of spots showing enhanced intensity for that particular plate. This was performed for a set of 32 plates as well as their pooled rows and columns. Thus, we have mapped individual **RLGS** spots to exact plate, row, and column addresses in the library and have thereby obtained immediate access to these clones. The feasibility of the technique is demonstrated in examples of cloning **methylated** DNA fragments identified in human breast tumor and testicular tumor **RLGS** profiles and in the cloning of an amplified DNA fragment identified in a human medulloblastoma **RLGS** profile.

L4 ANSWER 4 OF 37 MEDLINE on STN
AN 1999419917 MEDLINE
DN 99419917 PubMed ID: 10492168
TI Isolation of NotI clusters hypomethylated in HBV-integrated hepatocellular carcinomas by two-dimensional electrophoresis.
AU Nagai H; Baba M; Konishi N; Kim Y S; Nogami M; Okumura K; Emi M; Matsubara K
CS Institute for Molecular and Cellular Biology, Osaka University, Suita, Japan.
SO DNA RESEARCH, **(1999 Aug 31)** 6 (4) 219-25.
Journal code: 9423827. ISSN: 1340-2838.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-Y10751; GENBANK-Y10752
EM 199910
ED Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991014

AB To examine genetic and epigenetic alterations associated with HBV integration in hepatocarcinogenesis, we compared genomic DNA profiles of primary hepatocellular carcinomas (HCCs) and cell lines that either contained or did not contain integrated HBV. To accomplish this, we carried out **Restriction Landmark Genomic Scanning** (**RLGS**), a two-dimensional system that displays 2000-3000 Not I landmark sites in a single gel electrophoresis experiment. We identified one Not I landmark spot that showed high signal intensity in HBV-integrated cell lines or in primary HCCs, but not in HCCs or tumor-cell lines free of HBV integration. Cloning of this spot revealed that it consisted of a Not I cluster sequence enriched with CpG dinucleotides. This sequence, hypomethylated in association with HBV integration, was found in the peri-centromeric region of human acrochromosomes. The results demonstrate that epigenetic changes at specific sequences in the genome occur in association with HBV integration during the process of hepatocarcinogenesis.

L4 ANSWER 5 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:38394 BIOSIS
DN PREV200000038394
TI Cytosine **methylation** pattern in the sphingosine kinase gene locus relates to the expression of the splicing variants.
AU Imamura, Takuya [Reprint author]; Ohgane, Jun [Reprint author]; Tanaka, Satoshi [Reprint author]; Shiota, Kunio [Reprint author]
CS University of Tokyo, 1-1-1 Yayoi Bunkyo-Ku, Tokyo, 113-8657, Japan
SO Molecular Biology of the Cell, (Nov., 1999) Vol. 10, No. SUPPL., pp. 99a. print.
Meeting Info.: 39th Annual Meeting of the American Society for Cell Biology. Washington, D.C., USA. December 11-15, 1999. The American Society for Cell Biology.
CODEN: MBCEEV. ISSN: 1059-1524.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 19 Jan 2000
Last Updated on STN: 31 Dec 2001

L4 ANSWER 6 OF 37 MEDLINE on STN DUPLICATE 4
AN 1999443876 MEDLINE
DN 99443876 PubMed ID: 10512684
TI Detection and cloning of an X-linked locus associated with a NotI site that is not **methylated** on mouse inactivated X chromosome by the **RLGS**-M method.
AU Takada S; Kamiya M; Arima T; Kagebayashi H; Shibata H; Muramatsu M; Chapman V M; Wake N; Hayashizaki Y; Takagi N
CS Graduate School of Environmental Earth Science, Hokkaido University, North 10 West 5 Kita-ku, Sapporo, 060-0810, Japan.
SO GENOMICS, **(1999 Oct 1)** 61 (1) 92-100.
Journal code: 8800135. ISSN: 0888-7543.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AB019028; GENBANK-AB019029
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991109
AB In looking for genes that escape X chromosome inactivation, we scanned the **methylation** status of genomic DNA from XX, X0, and XY mice using the method of **restriction landmark genomic scanning** using **methylation**-sensitive endonuclease. We detected and cloned a candidate locus and identified the Orf1 gene. Orf1 has sequence similarities to the B2 repetitive element and human CXORF4

(formerly called EXLM1), which escapes X inactivation. The B2 element spans the 3' terminus of the ORF and the 3' UTR of Orf1. The Orf1 gene encompasses 18.5 kb of genomic DNA including 11 exons and 10 introns. Taking advantage of genomic polymorphisms present between MSM and C3H/He, we showed that murine Orf1 is mapped to the proximal region of the X chromosome. Despite the unmethylation of the NotI site, Orf1 is subject to X inactivation.

L4 ANSWER 7 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 2000:427588 BIOSIS
DN PREV200000427588
TI Epigenetic control of cellular differentiation and development by **methylation** of genomic DNA.
AU Shiota, Kunio [Reprint author]; Ohgane, Jun [Reprint author]
CS Laboratory of Cellular Biochemistry, Animal Resource Science/Veterinay Medical Science, University of Tokyo, Tokyo, 113-8657, Japan
SO Journal of Reproduction and Development, (December, 1999) Vol. 45, No. Supplement, pp. j51-j60. print.
ISSN: 0916-8818.
DT Article
LA Japanese
ED Entered STN: 4 Oct 2000
Last Updated on STN: 10 Jan 2002
AB The level of overall **methylation** of genomic DNA changes during the developmental process. Formation of 5-methyl-cytosine occurs by **methylation** of a cytosine base in DNA at CpG dinucleotides in vertebrates, and once acquired, it tends to be transmitted through cell division. In general, the DNA of inactive genes is more heavily **methylated** than that of active genes, and most observations are consistent with the idea that DNA **methylation** in vertebrates is associated with gene inactivation. Analysis of CpG island **methylation** pattern in the placenta and kidney by **Restriction Landmark Genomic Scanning** revealed that there were several CpG islands (2-3% of total CpG islands) that differed in **methylation** dependent on the tissues. Since it is estimated that there are 3-40,000 CpG islands in mammalian genome, the total number of such tissue-specific CpG islands is estimated as 7-800 per genome. This number of possible loci, tissue-specifically modified by **methylation**, is more than that of imprinted genes. The establishment of **methylation** pattern is thought to be essential for normal embryonic development. In this paper, we will review the epigenetic control of cellular differentiation by **methylation** of genomic DNA.

L4 ANSWER 8 OF 37 MEDLINE on STN DUPLICATE 5
AN 1999453756 MEDLINE
DN 99453756 PubMed ID: 10524231
TI A novel sperm-specific hypomethylation sequence is a demethylation hotspot in human hepatocellular carcinomas.
AU Nagai H; Kim Y S; Yasuda T; Ohmachi Y; Yokouchi H; Monden M; Emi M; Konishi N; Nogami M; Okumura K; Matsubara K
CS Institute for Molecular and Cellular Biology, Osaka University, Japan.
SO GENE, **(1999 Sep 3)** 237 (1) 15-20.
Journal code: 7706761. ISSN: 0378-1119.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-Y10752
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991102

AB Certain human DNA regions are strikingly undermethylated at CpG sites in sperm compared to adult somatic tissues. These sperm-specific hypomethylation sequences are thought to function early in embryogenesis or gametogenesis. By using the **restriction landmark genomic scanning** (**RLGS**) cloning method, we have isolated a novel sperm-specific hypomethylation sequence, the status of which changes during spermatogenesis, embryonal growth and differentiation. This sequence is a part of a new 'NotI repeat' consisting of a 1.4 kb repetitive unit sequence named DE-1. The sequence is GC-rich and has high homology to a CpG DNA clone that was isolated by a methyl CpG protein binding column, indicating that it was normally highly **methylated**. We investigated the **methylation** status of this sequence. In the normal genome the sequence was **methylated**, but in the human hepatocellular carcinoma (HCC) genome, the target sequence was demethylated at the cytosine residue of the CpG dinucleotides with high frequency (75% in the previous study). These data suggest that this regional DNA hypomethylation may play a role in both cell differentiation and hepatocarcinogenesis.

L4 ANSWER 9 OF 37 MEDLINE on STN DUPLICATE 6
AN 1998374301 MEDLINE
DN 98374301 PubMed ID: 9707596
TI The human GNAS1 gene is imprinted and encodes distinct paternally and biallelically expressed G proteins.
AU Hayward B E; Kamiya M; Strain L; Moran V; Campbell R; Hayashizaki Y; Bonthron D T
CS Human Genetics Unit, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, United Kingdom.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1998 Aug 18)** 95 (17) 10038-43.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AJ224867; GENBANK-AJ224868
EM 199809
ED Entered STN: 19980925
Last Updated on STN: 20000303
Entered Medline: 19980917
AB The GNAS1 gene encodes the alpha subunit of the G protein Gs, which couples receptor binding by several hormones to activation of adenylate cyclase. Null mutations of GNAS1 cause pseudohypoparathyroidism (PHP) type Ia, in which hormone resistance occurs in association with a characteristic osteodystrophy. The observation that PHP Ia almost always is inherited maternally has led to the suggestion that GNAS1 may be an imprinted gene. Here, we show that, although Gsalpha expression (directed by the promoter upstream of exon 1) is biallelic, GNAS1 is indeed imprinted in a promoter-specific fashion. We used parthenogenetic lymphocyte DNA to screen by **restriction landmark genomic scanning** for loci showing differential **methylation** between paternal and maternal alleles. This screen identified a region that was found to be **methylated** exclusively on a maternal allele and was located approximately 35 kb upstream of GNAS1 exon 1. This region contains three novel exons that are spliced into alternative GNAS1 mRNA species, including one exon that encodes the human homologue of the large G protein XLalphas. Transcription of these novel mRNAs is exclusively from the paternal allele in all tissues examined. The differential imprinting of separate protein products of GNAS1 therefore may contribute to the anomalous inheritance of PHP Ia.

L4 ANSWER 10 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:379880 BIOSIS
DN PREV199800379880

TI **Methylation** status of genomic DNA during differentiation of trophoblast giant cells: Analysis of rat choriocarcinoma cell line by **restriction landmark genomic scanning** (**RLGS**).
AU Ohgane, J.; Ogawa, T.; Shiota, K.
CS Lab. Cell. Biochem., Anim. Resource Sci/Vet Med. Sci., Univ. Tokyo, Tokyo, Japan
SO Biology of Reproduction, (1998) Vol. 58, No. SUPPL. 1, pp. 163. print.
Meeting Info.: Thirty-first Annual Meeting of the Society for the Study of Reproduction. College Station, Texas, USA. August 8-11, 1998. Society for the Study of Reproduction.
CODEN: BIREBV. ISSN: 0006-3363.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 22 Dec 1998
Last Updated on STN: 22 Dec 1998

=> d 11-20 bib ab

L4 ANSWER 11 OF 37 MEDLINE on STN DUPLICATE 7
AN 1998242386 MEDLINE
DN 98242386 PubMed ID: 9581285
TI Analysis of CpG islands of trophoblast giant cells by **restriction landmark genomic scanning**.
AU Ohgane J; Aikawa J; Ogura A; Hattori N; Ogawa T; Shiota K
CS Laboratory of Cellular Biochemistry, Animal Resource Science/Veterinary Medical Science, University of Tokyo, Japan.
SO DEVELOPMENTAL GENETICS, **(1998)** 22 (2) 132-40.
Journal code: 7909963. ISSN: 0192-253X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199805
ED Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980526
AB Rat trophoblast giant cells each contain at least 100 times more genomic DNA per nucleus than diploid cells. This unusual phenomenon appears to be of interest in relation to the molecular mechanism of cell differentiation and gene expression in the placenta. In the present study, we analyzed the CpG islands of trophoblast giant cells by **restriction landmark genomic scanning** (**RLGS**) using the **methylation**-sensitive landmark enzymes, Not I and Bss HII. More than 1,000 and 1,900 spots were detected by **RLGS** using Not I and Bss HII, respectively, in the placental junctional zone, where more than 90% of genomic DNA is present in the cells with higher DNA content. Of these, 97% (1,009 spots) and 99% (1,911 spots) of the spots found in the junctional zone showed an identical pattern and identical intensity with those of diploid cell controls, for which genomic DNA was extracted from the labyrinth zone and maternal kidney. Therefore, the giant cells are basically polyploid. More importantly, 24 tissue-specific spots were detected by **RLGS** using Not I. Subsequent cloning and sequencing of four typical spots of the genomic DNA confirmed that these DNA fragments contained abundant CpG dinucleotides and showed characteristics of CpG islands. Of these 24 spots, there were ten spots specific for the placenta, and three of them were specific for the junctional zone, indicating that **methylation** status of CpG islands in the placental tissue differed between the junctional zone and labyrinth zone. These results suggest that multiple rounds of endoreduplication and modification of CpG islands by cytosine

methylation occur during the differentiation process of giant cells.

L4 ANSWER 12 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:194504 BIOSIS
DN PREV199800194504
TI Identification and analysis of gene-associated CpG islands which are frequent targets of abnormal **methylation** in low grade human gliomas by two-dimension genome scanning.
AU Costello, Joseph F. [Reprint author]; Plass, Christoph; Smiraglia, Dominic; Nishikawa, Ryo; Berger, Mitchell S.; Huang, H.-J. Su [Reprint author]; Cavenee, Webster K. [Reprint author]
CS Ludwig Inst. Cancer Res., La Jolla, CA 92093-0660, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1998) Vol. 39, pp. 93. print.
Meeting Info.: 89th Annual Meeting of the American Association for Cancer Research. New Orleans, Louisiana, USA. March 28-April 1, 1998. American Association for Cancer Research.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 4 May 1998
Last Updated on STN: 4 May 1998

L4 ANSWER 13 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:194505 BIOSIS
DN PREV199800194505
TI Genome scanning for aberrant **methylation** in acute myeloid leukemia.
AU Plass, C. [Reprint author]; Yu, F.; Yu, L.; Smiraglia, D.; El-Rafai, W.; Knuutila, S.; Strout, M. P.; Held, W.; Caligiuri, M. A.
CS Ohio State Univ., Columbus, OH 43210, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1998) Vol. 39, pp. 93. print.
Meeting Info.: 89th Annual Meeting of the American Association for Cancer Research. New Orleans, Louisiana, USA. March 28-April 1, 1998. American Association for Cancer Research.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 4 May 1998
Last Updated on STN: 4 May 1998

L4 ANSWER 14 OF 37 MEDLINE on STN DUPLICATE 8
AN 97384968 MEDLINE
DN 97384968 PubMed ID: 9242463
TI **Restriction landmark genomic scanning** (**RLGS**-M)-based genome-wide scanning of mouse liver tumors for alterations in DNA **methylation** status.
AU Akama T O; Okazaki Y; Ito M; Okuizumi H; Konno H; Muramatsu M; Plass C; Held W A; Hayashizaki Y
CS Genome Science Laboratory, The Physical and Chemical Research (RIKEN), Tsukuba, Ibaraki, Japan.
NC RO1-CA686612 (NCI)
SO CANCER RESEARCH, **(1997 Aug 1)** 57 (15) 3294-9.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
ED Entered STN: 19970922

Last Updated on STN: 19980206
Entered Medline: 19970911

AB **Restriction landmark genomic scanning** for **methylation** (**RLGS**-M) was used to detect, and subsequently clone, genomic regions with alterations in DNA **methylation** associated with tumorigenesis. Use of a **methylation**-sensitive enzyme for the landmark cleavage allows analysis of changes in **methylation** patterns. In this study, we used **RLGS**-M to analyze SV40 T antigen-induced mouse liver tumors derived from interspecific F1 hybrids between Mus spretus (S) and C57BL/6 (B6). Because 575 S- and B6-specific **RLGS** loci/spots have been mapped, tumor-related alterations in the **RLGS** profile could be immediately localized to specific chromosomal regions. We previously found that the loss of contiguous loci/spots could be attributed primarily to DNA loss, whereas loss of solitary loci/spots could be attributed primarily to DNA **methylation**. In this study, we examined 30 mouse liver tumor samples for loss of the 507 mapped loci/spots. Fourteen solitary loci/spots found to be absent or reduced in more than 75% of tumor samples were cloned and subjected to DNA sequence analyses. Two loci were identified as alpha4 integrin and p16/CDKN2, genes reported to be involved in tumorigenesis. Thus, **RLGS**-M can detect alterations in the **methylation** status of known tumor suppressor genes and provide a method for detecting and subsequently cloning novel genomic regions that undergo alterations in **methylation** during tumorigenesis.

L4 ANSWER 15 OF 37 MEDLINE on STN
AN 1998074512 MEDLINE
DN 98074512 PubMed ID: 9413032
TI Genetic changes in prostate cancer.
AU Konishi N; Cho M; Yamamoto K; Hiasa Y
CS Second Department of Pathology, Nara Medical University, Japan.. nkonishi@nmu-gw.cc.naramed-u.ac.jp
SO PATHOLOGY INTERNATIONAL, **(1997 Nov)** 47 (11) 735-47.
Journal code: 9431380. ISSN: 1320-5463.
CY Australia
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980206
Last Updated on STN: 19980206
Entered Medline: 19980129

AB Recent advances in molecular biology have allowed us to understand that it is the accumulation of genetic alterations which leads to each step of tumorigenesis. What the specific alterations may be, however, often varies with each neoplasm. Prostate cancer is somewhat unique in its presentation to the pathologist of a bewildering array of histologies difficult to assign to diagnostic categories and contributing to misinterpretations of underlying molecular events. As with any malignancy, it is of utmost importance to thoroughly analyze and record the genetic aberrations found in prostate cancer with the objective of correlation to the pathology and natural history of the disease. Multiple oncogenes and tumor suppressor genes have been investigated in both clinical and latent cancer using conventional mutational analyses. To probe deeper into these genes and to uncover novel molecular events, genomic tumor DNA were examined using **restriction landmark genomic scanning** (**RLGS**), a method which allows the identification and comparison of specific genetic alterations within large segments and multiple samples of DNA at a time. This article reviews what has been identified based on numerous molecular studies, focusing on the genetic alterations peculiar to human prostate cancer.

L4 ANSWER 16 OF 37 MEDLINE on STN DUPLICATE 9
AN 97154506 MEDLINE
DN 97154506 PubMed ID: 9001224
TI A unique downregulation of h2-calponin gene expression in Down syndrome: a possible attenuation mechanism for fetal survival by **methylation** at the CpG island in the trisomic chromosome 21.
AU Kuromitsu J; Yamashita H; Kataoka H; Takahara T; Muramatsu M; Sekine T; Okamoto N; Furuichi Y; Hayashizaki Y
CS Genome Science Laboratory, RIKEN Tsukuba Life Science Center, The Institute of Physical and Chemical Research (RIKEN), Tsukuba, Ibaraki, Japan.
SO MOLECULAR AND CELLULAR BIOLOGY, **(1997 Feb)** 17 (2) 707-12.
Journal code: 8109087. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-D86058; GENBANK-D86059
EM 199702
ED Entered STN: 19970305
Last Updated on STN: 19990129
Entered Medline: 19970218
AB To understand the effect of trisomic chromosome 21 on the cause of Down syndrome (DS), DNA **methylation** in the CpG island, which regulates the expression of adjacent genes, was investigated with the DNAs of chromosome 21 isolated from DS patients and their parents. A **methylation**-sensitive enzyme, BssHII, was used to digest DNAs of chromosome 21, and the resulting DNA fragments were subjected to **RLGS (restriction landmark genomic scanning)**. Surprisingly, the CpG island of the h2-calponin gene was shown to be specifically **methylated** by comparative studies with **RLGS** and Southern blot analysis. In association with this **methylation**, h2-calponin gene expression was attenuated to the normal level, although other genes in the DS region of chromosome 21 were expressed dose dependently at 1.5 times the normal level. These results and the high miscarriage rate associated with trisomy 21 embryos imply that the altered in vivo **methylation** that attenuates downstream gene expression, which is otherwise lethal, permits the generation of DS neonates. The h2-calponin gene detected by the **RLGS** procedure may be one such gene that is attenuated.

L4 ANSWER 17 OF 37 MEDLINE on STN
AN 97411469 MEDLINE
DN 97411469 PubMed ID: 9266447
TI Analyses of human gliomas by **restriction landmark genomic scanning**.
AU Nakamura M; Konishi N; Tsunoda S; Hiasa Y; Tsuzuki T; Aoki H; Kobitsu K; Nagai H; Sakaki T
CS Department of Neurosurgery, Nara Medical University, Kashihara, Japan.
SO JOURNAL OF NEURO-ONCOLOGY, **(1997 Nov)** 35 (2) 113-20.
Journal code: 8309335. ISSN: 0167-594X.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
ED Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971027
AB The 16 primary gliomas were examined for changes in genomic DNA using a recently developed 2-dimensional gel electrophoresis method called **restriction landmark genomic scanning (RLGS)**. This approach allows detection of DNA amplification, deletion, **methylation** and potentially other genetic

rearrangements represented as decreases and increases in spot/fragment intensity on an autoradiogram. Approximately 2,000 landmark sites in tumor DNA were compared with those of DNA isolated from normal brain tissues. Seven spots showing intensified signal were consistently detected in at least 50% of tumors, implying activation of corresponding DNA sequences, and 8 additional spots having reduced signal were observed, again in more than 50% of all tumors, suggesting inactivation by the loss of 1 allele or homozygous deletion. Decreased signal may also infer relative CpG island **methylation** state. Of those spots consistently identified in tumors, 2 amplified and 4 reduced spots were found to be characteristic of low- and high-grade tumors, while the remaining 5 amplified and 4 reduced spots were associated with high-grade gliomas only, suggesting a link of specific mutations to degree of malignancy. A separate subset of glioblastomas evaluated, however, showed no alterations in these 'hot spots' which were detected in even low grade astrocytomas. The results demonstrate the genetic heterogeneity of glioblastoma and implicate the progression of neoplasia via differing genetic pathways.

L4 ANSWER 18 OF 37 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:66572 BIOSIS
DN PREV199800066572
TI Genomic scanning for aberrant **methylation** in acute myeloid leukemia: Involvement of WIT-1 **methylation** at relapse.
AU Plass, C.; Yu, F.; Yu, L.; Trout, M. P.; Held, W. A.; Caligiuri, M. A.
CS Div. Human Cancer Genetics, Arthur G. James Cancer Hosp., Ohio State Univ., Columbus, OH, USA
SO Blood, (Nov. 15, 1997) Vol. 90, No. 10 SUPPL. 1 PART 1, pp. 60A-61A. print.
Meeting Info.: 39th Annual Meeting of the American Society of Hematology. San Diego, California, USA. December 5-9, 1997. The American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 30 Jan 1998
Last Updated on STN: 30 Jan 1998

L4 ANSWER 19 OF 37 MEDLINE on STN
AN 1998033929 MEDLINE
DN 98033929 PubMed ID: 9384797
TI Genomic alterations of human gliomas detected by **restriction landmark genomic scanning**.
AU Nakamura M; Konishi N; Tsunoda S; Hiasa Y; Takemura K; Tsuzuki T; Kobitsu K; Sakaki T
CS Department of Neurosurgery, Nara Medical University, Japan.. nkonishi@nmu-gw.cc.naramed-u.ac.jp
SO BRAIN TUMOR PATHOLOGY, **(1997)** 14 (1) 13-7.
Journal code: 9716507. ISSN: 1433-7398.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980206
Last Updated on STN: 19980206
Entered Medline: 19980126
AB Alterations of genomic DNA in eight primary astrocytic tumors and two glioma cell lines were examined using a recently developed two-dimensional gel electrophoresis method called **restriction landmark genomic scanning (RLGS)**. **RLGS** allows us to detect amplifications, deletions, and **methylation**

in genomic DNA in one procedure without requiring any polymorphic markers. Approximately 2000 spots (landmark sites) in tumor specimens were compared with those in normal brain tissue. The 10 spots with intensified signal were reproducibly detected in at least 50% of primary tumors, implying amplification of corresponding DNA sequences. Conversely, 12 spots with reduced signal were observed in more than 50% of all tumors, suggesting inactivation by allelic loss, homozygous deletion, or CpG island **methylation**. These results suggest that common genetic alterations are closely correlated with the genesis or progression of human gliomas.

L4 ANSWER 20 OF 37 MEDLINE on STN DUPLICATE 10
AN 97115677 MEDLINE
DN 97115677 PubMed ID: 8954993
TI Stac, a novel neuron-specific protein with cysteine-rich and SH3 domains.
AU Suzuki H; Kawai J; Taga C; Yaoi T; Hara A; Hirose K; Hayashizaki Y; Watanabe S
CS Shionogi Institute for Medical Science, Mishima 2-5-1, Settsu-shi, Osaka, 566, Japan.. sachihiko.watanabe@shionogi.co.jp
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1996 Dec 24)** 229 (3) 902-9.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-D86639; GENBANK-D86640
EM 199701
ED Entered STN: 19970219
Last Updated on STN: 20000303
Entered Medline: 19970130
AB In **RLGS**-M (**restriction landmark genomic scanning** using **methylation**-sensitive endonuclease) displays of mouse brains, spot #91 is one of tissue-specific gel spots whose intensity changes developmentally. We have now cloned the corresponding cDNA from this spot and analyzed its structure and expression. The deduced amino acid sequence revealed that the #91 cDNA encodes a novel protein of 403 amino acids which consists of a cysteine-rich domain and a SH3 domain. We designated this gene as Stac. Northern blotting and in situ hybridization analyses demonstrated that 2.7 kb of Stac mRNA is expressed predominantly in brain and neurons, especially in hippocampus, cerebellum and inferior olive. Further, the gene product of 47 kDa was found by western blotting analysis in the soluble fractions of brain as well as Stac-expression vector-transfected NIH3T3 cells. Although the function of Stac is unknown so far, it is likely involved in a neuron-specific signal transduction.

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=> s stem cells and methylation
L1 448 STEM CELLS AND METHYLATION

=> s l1 and py<2000
L2 257 L1 AND PY<2000

=> s l2 and review
L3 5 L2 AND REVIEW

=> d 1-5 bib ab

L3 ANSWER 1 OF 5 MEDLINE on STN
AN 1998412076 MEDLINE
DN 98412076 PubMed ID: 9739759
TI Progress in understanding the molecular pathogenesis of human lung cancer.
AU Sekido Y; Fong K M; Minna J D
CS Hamon Center for Therapeutic Oncology Research, University of Texas Southwestern Medical Center, Dallas 75235-8593, USA.
NC P50 CA70907 (NCI)
SO BIOCHIMICA ET BIOPHYSICA ACTA, **(1998 Aug 19)** 1378 (1) F21-59.
Ref: 324
Journal code: 0217513. ISSN: 0006-3002.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199809
ED Entered STN: 19981006
Last Updated on STN: 19981006
Entered Medline: 19980924
AB We **review** the molecular pathogenesis of lung cancer including alterations in dominant oncogenes, recessive oncogenes/tumor suppressor genes, alterations in growth regulatory signaling pathways, abnormalities in other pathways, such as apoptosis, autocrine and paracrine growth stimulatory loops, angiogenesis, and host immune responses, other mechanisms of genetic changes, such as microsatellite and **methylation** alterations, and the potential for inherited predisposition to lung cancer. These changes are related to multistage carcinogenesis involving preneoplastic lesions, and lung development and differentiation. The translational applications of these findings for developing new ways of early detection, prevention, treatment, and prognosis of lung cancer are discussed.

L3 ANSWER 2 OF 5 MEDLINE on STN
AN 1998238809 MEDLINE
DN 98238809 PubMed ID: 9571078
TI Analysis and identification of imprinted genes.
AU Kelsey G; Reik W
CS Laboratory of Developmental Genetics and Imprinting, Babraham Institute, Cambridge, United Kingdom.
SO METHODS, **(1998 Feb)** 14 (2) 211-34.
Journal code: 9426302. ISSN: 1046-2023.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 199806
ED Entered STN: 19980713
Last Updated on STN: 19980713
Entered Medline: 19980626
AB Genomic imprinting in mammals results in the unequal expression of the two parental alleles of specific genes. The existence of imprinting in the mouse emerged from nuclear transplantation studies and from the abnormal phenotypes associated with uniparental inheritance of particular chromosome segments. Over the past 5 years, 20 or so imprinted genes have been identified. This has emphasized the important roles played by some imprinted genes in development, permitted a description of the epigenetic properties associated with imprinting, and provided the first insights into the regulation of imprinting. In this article, we discuss the generation of experimental material in which imprinting effects can be analyzed, **review** the properties of imprinted genes, and discuss how to examine them using state-of-the-art techniques. Finally, we consider the means by which new imprinted genes can be identified.

L3 ANSWER 3 OF 5 MEDLINE on STN
AN 1998160556 MEDLINE
DN 98160556 PubMed ID: 9499581
TI Histone acetylation and X inactivation.
AU Keohane A M; Lavender J S; O'Neill L P; Turner B M
CS Department of Anatomy, University of Birmingham Medical School, Edgbaston, U.K.
SO DEVELOPMENTAL GENETICS, **(1998)** 22 (1) 65-73. Ref: 61
Journal code: 7909963. ISSN: 0192-253X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199803
ED Entered STN: 19980410
Last Updated on STN: 19980410
Entered Medline: 19980330
AB In mammals, the levels of X-linked gene products in males and females are equalised by the silencing, early in development, of most of the genes on one of the two female X chromosomes. Once established, the silent state is stable from one cell generation to the next. In eutherian mammals, the inactive X chromosome (Xi) differs from its active homologue (Xa) in a number of ways, including increased **methylation** of selected CpGs, replication late in S-phase, expression of the Xist gene with binding of Xist RNA and underacetylation of core histones. The latter is a common property of genetically inactive chromatin but, in the case of Xi, it is not clear whether it is an integral part of the silencing process or simply a consequence of some other property of Xi, such as late replication. The present **review** describes two approaches that address this problem. The first shows that Xi in marsupial mammals also contains underacetylated H4, even though its properties differ widely from those of the eutherian Xi. The continued presence of histone underacetylation on Xi in these evolutionarily distant mammals argues for its fundamental importance. The second approach uses mouse embryonic **stem cells** and places H4 deacetylation in a sequence of events leading to complete X inactivation. The results argue that histone underacetylation plays a role in the stabilisation of the inactive state, rather than in its initiation.

L3 ANSWER 4 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:256466 BIOSIS
DN PREV199800256466
TI Analysis and identification of imprinted genes.
AU Kelsey, Gavin; Reik, Wolf

CS Lab. Developmental Genetics Imprinting, Babraham Inst., Babraham, Cambridge CB2 4AT, UK
SO Methods (Orlando), (Feb., 1998) Vol. 14, No. 2, pp. 211-234. print. CODEN: MTHDE9. ISSN: 1046-2023.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 9 Jun 1998
Last Updated on STN: 9 Jun 1998
AB Genomic imprinting in mammals results in the unequal expression of the two parental alleles of specific genes. The existence of imprinting in the mouse emerged from nuclear transplantation studies and from the abnormal phenotypes associated with uniparental inheritance of particular chromosome segments. Over the past 5 years, 20 or so imprinted genes have been identified. This has emphasized the important roles played by some imprinted genes in development, permitted a description of the epigenetic properties associated with imprinting, and provided the first insights Into the regulation of imprinting. In this article, we discuss the generation of experimental material in which imprinting effects can be analyzed, **review** the properties of imprinted genes, and discuss how to examine them using state-of-the-art techniques. Finally, we consider the means by which new imprinted genes can be identified.

L3 ANSWER 5 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:165496 BIOSIS
DN PREV199800165496
TI Histone acetylation and X inactivation.
AU Keohane, Ann M.; Lavender, Jayne S.; O'Neill, Laura P.; Turner, Bryan M. [Reprint author]
CS Chromatin Gene Expression Group, Dep. Anatomy, Univ. Birmingham Med. Sch., Edgbaston, Birmingham B15 2TT, UK
SO Developmental Genetics, (1998) Vol. 22, No. 1, pp. 65-73. print. CODEN: DGNTDW. ISSN: 0192-253X.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 6 Apr 1998
Last Updated on STN: 6 Apr 1998
AB In mammals, the levels of X-linked gene products in males and females are equalised by the silencing, early in development, of most of the genes on one of the two female X chromosomes. Once established, the silent state is stable from one cell generation to the next. In eutherian mammals, the inactive X chromosome (Xi) differs from its active homologue (Xa) in a number of ways, including increased **methylation** of selected CpGs, replication late in S-phase, expression of the Xist gene with binding of Xist RNA and underacetylation of core histones. The latter is a common property of genetically inactive chromatin but, in the case of Xi, it is not clear whether it is an integral part of the silencing process or simply a consequence of some other property of Xi, such as late replication. The present **review** describes two approaches that address this problem. The first shows that Xi in marsupial mammals also contains underacetylated H4, even though its properties differ widely from those of the eutherian Xi. The continued presence of histone underacetylation on Xi in these evolutionarily distant mammals argues for its fundamental importance. The second approach uses mouse embryonic **stem cells** and places H4 deacetyation in a sequence of events leading to complete X inactivation. The results argue that histone underacetylation ploys a role in the stabilisation of the inactive state, rather than in its initiation.

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FILE 'MEDLINE, BIOSIS' ENTERED AT 13:46:08 ON 17 DEC 2003
L1 448 S STEM CELLS AND METHYLATION
L2 257 S L1 AND PY<2000
L3 5 S L2 AND REVIEW

=> s l2 and restriction
L4 53 L2 AND RESTRICTION

=> s l2 and ((restriction landmark genomic scanning) or rlgs)
L5 0 L2 AND ((RESTRICTION LANDMARK GENOMIC SCANNING) OR RLGS)

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L6 189 DUPLICATE REMOVE L2 (68 DUPLICATES REMOVED)

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L6 ANSWER 1 OF 189 MEDLINE on STN DUPLICATE 1
AN 2000062851 MEDLINE
DN 20062851 PubMed ID: 10593928
TI Tandem B1 elements located in a mouse **methylation** center provide a target for de novo DNA **methylation**.
AU Yates P A; Burman R W; Mummaneni P; Krussel S; Turker M S
CS Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University, Portland, Oregon 97201, USA.
NC T32
SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1999 Dec 17)** 274 (51) 36357-61.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200001
ED Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127
AB A cis-acting **methylation** center that signals de novo DNA **methylation** is located upstream of the mouse Aprt gene. In the current study, two approaches were taken to determine if tandem B1 repetitive elements found at the 3' end of the **methylation** center contribute to the **methylation** signal. First, bisulfite genomic sequencing demonstrated that CpG sites within the B1 elements were methylated at relative levels of 43% in embryonal **stem cells** deficient for the maintenance DNA methyltransferase when compared with wild type embryonal **stem cells**. Second, the ability of the B1 elements to signal de novo **methylation** upon stable transfection into mouse embryonal carcinoma cells was examined. This approach demonstrated that the B1 elements were methylated de novo to a high level in the embryonal carcinoma cells and that the B1 elements acted synergistically. The results from these experiments provide strong evidence that the tandem B1 repetitive elements provide a significant fraction of the **methylation** center signal. By extension, they also support the hypothesis that one role for DNA **methylation** in mammals is to protect the genome from expression

and transposition of parasitic elements.

L6 ANSWER 2 OF 189 MEDLINE on STN DUPLICATE 2
AN 1999377061 MEDLINE
DN 99377061 PubMed ID: 10446198
TI Factors affecting de novo **methylation** of foreign DNA in mouse embryonic **stem cells**.
AU Hertz J M; Schell G; Doerfler W
CS Institute of Genetics, University of Cologne, D-50931 Koeln, Germany.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, **(1999 Aug 20)** 274 (34) 24232-40.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199909
ED Entered STN: 19990921
Last Updated on STN: 19990921
Entered Medline: 19990909
AB Integration of foreign DNA into an established host genome can lead to changes in **methylation** in both the inserted DNA and in host sequences and potentially alters transgene and cellular transcription patterns. This work addresses the questions of what factors influence de novo **methylation**, and whether the integration site or inserted DNA can affect de novo **methylation**. Homologous recombination was used to integrate foreign DNA into a specific gene, B lymphocyte kinase (BLK), in mouse embryonic stem (ES) cells. Two plasmids were chosen for integration; one contained the adenovirus type 2 E2AL promoter upstream of the luciferase reporter gene, and the second carried the early SV40 promoter. The **methylation** patterns were analyzed using HpaII and MspI restriction endonucleases for both homologously recombined and randomly integrated foreign DNA in the ES cell clones. Upon homologous reinsertion of the BLK gene into the genome of mouse ES cells, **methylation** patterns in this gene were reestablished. In DNA segments adjoined to the BLK gene, the de novo patterns of DNA **methylation** depended on the viral sequences in these clones and on the locations of the inserts, i.e. on whether the insertions resulted from homologously recombined or randomly integrated foreign DNA. In homologously recombined DNA, sequences carrying the adenovirus type 2 promoter were heavily methylated, and those with an SV40 promoter and an SV40 enhancer element remained unmethylated or hypomethylated. Upon removal of the enhancer element, these inserted constructs also became heavily methylated. In addition, all randomly integrated constructs were heavily methylated independently of the promoter and enhancer element present in the construct. These results indicate that modes and sites of integration as well as the inserted nucleotide sequence, possibly promoter strength, are factors affecting de novo **methylation**.

L6 ANSWER 3 OF 189 MEDLINE on STN
AN 1999248185 MEDLINE
DN 99248185 PubMed ID: 10229843
TI Evidence that the Igkappa gene MAR regulates the probability of premature V-J joining and somatic hypermutation.
AU Yi M; Wu P; Trevorrow K W; Claflin L; Garrard W T
CS Department of Molecular Biology and Oncology, University of Texas Southwestern Medical Center, Dallas, TX 75235, USA. b1.
NC AI09433 (NIAID)
GM29935 (NIGMS)
GM51585 (NIGMS)
SO JOURNAL OF IMMUNOLOGY, **(1999 May 15)** 162 (10) 6029-39.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199906
ED Entered STN: 19990628
Last Updated on STN: 19990628
Entered Medline: 19990614
AB The Igkappa gene contains an evolutionarily conserved nuclear matrix association region (MAR) adjacent to the intronic enhancer. To test for the function of this MAR, we created mouse lines with a targeted MAR deletion. In MAR knockout animals, the immune system was normal in nearly all respects, including the distributions of various B cell populations and Ab levels. However, in pro-B cells, enhanced rearrangement was noted on the MAR- allele in heterozygotes. In addition, the efficiencies for targeting and generating somatic mutations were reduced on MAR-deleted alleles. These results provide evidence for the MAR negatively regulating the probability of premature rearrangement and positively regulating the probability of somatic hypermutation.

L6 ANSWER 4 OF 189 MEDLINE on STN DUPLICATE 3
AN 1999292841 MEDLINE
DN 99292841 PubMed ID: 10364297
TI Amelioration of retroviral vector silencing in locus control region beta-globin-transgenic mice and transduced F9 embryonic cells.
AU Osborne C S; Pasceri P; Singal R; Sukonnik T; Ginder G D; Ellis J
CS Programs in Developmental Biology and Blood and Cancer Research, Hospital for Sick Children, Toronto, Ontario, Canada M5G 1X8.
NC R37-DK29902 (NIDDK)
SO JOURNAL OF VIROLOGY, **(1999 Jul)** 73 (7) 5490-6.
Journal code: 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199907
ED Entered STN: 19990806
Last Updated on STN: 19990806
Entered Medline: 19990723
AB Retroviral vectors are transcriptionally silenced in hematopoietic **stem cells**, and this phenomenon must be overcome for effective gene therapy of blood diseases. The murine stem cell virus (MSCV) vector completely silences beta-globin reporter genes regulated by locus control region (LCR) elements 5'HS2 to 5'HS4 in seven of eight transgenic mice. Here, we show that no single known MSCV silencer element is sufficient for complete LCR beta-globin transgene silencing. However, partial silencing of high-copy transgenes is conveyed by the MSCV direct repeat and promoter elements. The CpG **methylation** pattern of silenced and expressed MSCV promoter transgenes is virtually identical, demonstrating that silencing does not absolutely correlate with **methylation** status. Combined mutations in all four MSCV silencer elements leads to expression of beta-globin in 6 of 10 transgenic mice. The same mutations incorporated into the HSC1 retrovirus vector direct neo gene expression in 71% of transduced F9 embryonic carcinoma cells. These studies demonstrate that combined mutation of four retroviral silencer elements relieves complete silencing in most transgenic mice and transduced F9 cells and suggests that novel silencer elements remain. Enhanced expression of the HSC1 vector in primitive **stem cells** is well suited for blood gene therapy applications.

L6 ANSWER 5 OF 189 MEDLINE on STN
AN 2000021842 MEDLINE
DN 20021842 PubMed ID: 10553071
TI Early B cell factor is an activator of the B lymphoid kinase promoter in early B cell development.
AU Akerblad P; Sigvardsson M

CS Immunology Group, Cell and Molecular Biology, Lund University, Sweden.
SO JOURNAL OF IMMUNOLOGY, **(1999 Nov 15)** 163 (10) 5453-61.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991202
AB Early B cell factor (EBF) is a transcription factor suggested to be involved in the transcriptional control of several B cell restricted genes. EBF is also essential for B lymphocyte development because mice carrying a homologous disruption of the EBF gene lack mature B lymphocytes. This makes the identification of genetic targets for EBF important for the understanding of early B cell development. Examination of the nucleotide sequence of the B lymphoid kinase (Blk) promoter suggested the presence of an EBF binding site, and in vivo footprinting analysis showed that the site was protected from **methylation** in a pre-B cell line. EMSA indicated that recombinant and cellular EBF interact physically with this site; furthermore, transient transfections indicated that ectopic expression of EBF in nonlymphoid HeLa cells activate a Blk promoter-controlled reporter construct 9-fold. The defined EBF binding site was also important for the function of the Blk promoter in pre-B cells, because transient transfections of a reporter construct under the control of an EBF site-mutated Blk promoter displayed only 20-30% of the activity of the wild-type promoter. Furthermore, transient transfections in HeLa cells proposed that EBF and B cell-specific activator protein were able to cooperate in the activation of a Blk promoter-controlled reporter construct. These data indicate that EBF plays an important role in the regulation of the Blk promoter in early B cell development and that EBF and BSAP are capable to act in cooperation to induce a target gene.

L6 ANSWER 6 OF 189 MEDLINE on STN DUPLICATE 4
AN 2000021682 MEDLINE
DN 20021682 PubMed ID: 10552944
TI Improved expression in hematopoietic and lymphoid cells in mice after transplantation of bone marrow transduced with a modified retroviral vector.
AU Halene S; Wang L; Cooper R M; Bockstoce D C; Robbins P B; Kohn D B
CS Division of Research Immunology/Bone Marrow Transplantation, Childrens Hospital Los Angeles, Los Angeles, CA 90027, USA.
NC CA59318 (NCI)
SO BLOOD, **(1999 Nov 15)** 94 (10) 3349-57.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199911
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991130
AB Retroviral vectors based on the Moloney murine leukemia virus (MoMuLV) are currently the most commonly used vehicles for stable gene transfer into mammalian hematopoietic cells. But, even with reasonable transduction efficiency, expression only occurs in a low percentage of transduced cells and decreases to undetectable levels over time. We have previously reported the modified MND LTR (myeloproliferative sarcoma virus enhancer, negative control region deleted, dl587rev primer-binding site substituted) to show increased expression frequency and decreased **methylation** in transduced murine embryonic **stem cells** and

hematopoietic **stem cells**. We have now compared expression of the enhanced green fluorescent protein (eGFP) from a vector using the MoMuLV LTR (LeGFPSN) with that from the modified vector (MNDeGFPSN) in mature hematopoietic and lymphoid cells in the mouse bone marrow transplant (BMT) model. In primary BMT recipients, we observed a higher frequency of expression from the MND LTR (20% to 80%) in hematopoietic cells of all lineages in spleen, bone marrow, thymus, and blood compared with expression from the MoMuLV LTR (5% to 10%). Expression from the MND LTR reached 88% in thymic T lymphocytes and 54% in splenic B lymphocytes for up to 8 months after BMT. The mean fluorescence intensity of the individual cells, indicating the amount of protein synthesized, was 6- to 10-fold higher in cells expressing MNDeGFPSN compared with cells expressing LeGFPSN. Transduction efficiencies determined by DNA polymerase chain reaction of vector copy number were comparable for the 2 vectors. Therefore, the MND vector offers an improved vehicle for reliable gene expression in hematopoietic cells.

L6 ANSWER 7 OF 189 MEDLINE on STN
AN 1999298186 MEDLINE
DN 99298186 PubMed ID: 10369674
TI Activation of the erythropoietin receptor by the gp55-P viral envelope protein is determined by a single amino acid in its transmembrane domain.
AU Constantinescu S N; Liu X; Beyer W; Fallon A; Shekar S; Henis Y I; Smith S O; Lodish H F
CS Whitehead Institute for Biomedical Research, Nine Cambridge Center, Cambridge, MA 02142, USA.
NC HL32262 (NHLBI)
SO EMBO JOURNAL, **(1999 Jun 15)** 18 (12) 3334-47.
Journal code: 8208664. ISSN: 0261-4189.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199908
ED Entered STN: 19990827
Last Updated on STN: 19990827
Entered Medline: 19990819
AB The spleen focus forming virus (SFFV) gp55-P envelope glycoprotein specifically binds to and activates murine erythropoietin receptors (EpoRs) coexpressed in the same cell, triggering proliferation of erythroid progenitors and inducing erythroleukemia. Here we demonstrate specific interactions between the single transmembrane domains of the two proteins that are essential for receptor activation. The human EpoR is not activated by gp55-P but by mutation of a single amino acid, L238, in its transmembrane sequence to its murine counterpart serine, resulting in its ability to be activated. The converse mutation in the murine EpoR (S238L) abolishes activation by gp55-P. Computational searches of interactions between the membrane-spanning segments of murine EpoR and gp55-P provide a possible explanation: the face of the EpoR transmembrane domain containing S238 is predicted to interact specifically with gp55-P but not gp55-A, a variant which is much less effective in activating the murine EpoR. Mutational studies on gp55-P M390, which is predicted to interact with S238, provide additional support for this model. Mutation of M390 to isoleucine, the corresponding residue in gp55-A, abolishes activation, but the gp55-P M390L mutation is fully functional. gp55-P is thought to activate signaling by the EpoR by inducing receptor oligomerization through interactions involving specific transmembrane residues.

L6 ANSWER 8 OF 189 MEDLINE on STN DUPLICATE 5
AN 1999182442 MEDLINE
DN 99182442 PubMed ID: 10082521
TI Parental allele-specific chromatin configuration in a boundary-imprinting-control element upstream of the mouse H19 gene.

AU Khosla S; Aitchison A; Gregory R; Allen N D; Feil R
CS Programme in Developmental Genetics, The Babraham Institute, Cambridge CB2 4AT, United Kingdom.
SO MOLECULAR AND CELLULAR BIOLOGY, **(1999 Apr)** 19 (4) 2556-66.
Journal code: 8109087. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199904
ED Entered STN: 19990504
Last Updated on STN: 19990504
Entered Medline: 19990420
AB The mouse H19 gene is expressed from the maternal chromosome exclusively. A 2-kb region at 2 to 4 kb upstream of H19 is paternally methylated throughout development, and these sequences are necessary for the imprinted expression of both H19 and the 5'-neighboring Igf2 gene. In particular, on the maternal chromosome this element appears to insulate the Igf2 gene from enhancers located downstream of H19. We analyzed the chromatin organization of this element by assaying its sensitivity to nucleases in nuclei. Six DNase I hypersensitive sites (HS sites) were detected on the unmethylated maternal chromosome exclusively, the two most prominent of which mapped 2.25 and 2.75 kb 5' to the H19 transcription initiation site. Five of the maternal HS sites were present in expressing and nonexpressing tissues and in embryonic stem (ES) cells. They seem, therefore, to reflect the maternal origin of the chromosome rather than the expression of H19. A sixth maternal HS site, at 3.45 kb upstream of H19, was detected in ES cells only. The nucleosomal organization of this element was analyzed in tissues and ES cells by micrococcal nuclease digestion. Specifically on the maternal chromosome, an unusual and strong banding pattern was obtained, suggestive of a nonnucleosomal organization. From our studies, it appears that the unusual chromatin organization with the presence of HS sites (maternal chromosome) and DNA **methylation** (paternal chromosome) in this element are mutually exclusive and reflect alternate epigenetic states. In addition, our data suggest that nonhistone proteins are associated with the maternal chromosome and that these might be involved in its boundary function.

L6 ANSWER 9 OF 189 MEDLINE on STN
AN 1999428334 MEDLINE
DN 99428334 PubMed ID: 10498621
TI Cloning and characterization of EphA3 (Hek) gene promoter: DNA **methylation** regulates expression in hematopoietic tumor cells.
AU Dottori M; Down M; Huttmann A; Fitzpatrick D R; Boyd A W
CS Queensland Institute of Medical Research, Department of Medicine, Herston, Queensland, Australia.
SO BLOOD, **(1999 Oct 1)** 94 (7) 2477-86.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991104
AB The Eph family of receptor tyrosine kinases (RTK) has restricted temporal and spatial expression patterns during development, and several members are also found to be upregulated in tumors. Very little is known of the promoter elements or regulatory factors required for expression of Eph RTK genes. In this report we describe the identification and characterization of the EphA3 gene promoter region. A region of 86 bp located at -348 bp to -262 bp upstream from the transcription start site was identified as the basal promoter. This region was shown to be active in both

EphA3-expressing and -nonexpressing cell lines, contrasting with the widely different levels of EphA3 expression. We noted a region rich in CpG dinucleotides downstream of the basal promoter. Using Southern blot analyses with **methylation**-sensitive restriction enzymes and bisulfite sequencing of genomic DNA, sites of DNA **methylation** were identified in hematopoietic cell lines which correlated with their levels of EphA3 gene expression. We showed that EphA3 was not methylated in normal tissues but that a subset of clinical samples from leukemia patients showed extensive **methylation**, similar to that observed in cell lines. These results suggest that DNA **methylation** may be an important mechanism regulating EphA3 transcription in hematopoietic tumors.

L6 ANSWER 10 OF 189 MEDLINE on STN DUPLICATE 6
AN 1999263031 MEDLINE
DN 99263031 PubMed ID: 10325416
TI The human DNA methyltransferases (DNMTs) 1, 3a and 3b: coordinate mRNA expression in normal tissues and overexpression in tumors.
AU Robertson K D; Uzvolgyi E; Liang G; Talmadge C; Sumegi J; Gonzales F A; Jones P A
CS University of Southern California, Norris Comprehensive Cancer Center, MS 83, 1441 Eastlake Avenue, Los Angeles, CA 90033, USA.
NC R35 CA 49758 (NCI)
SO NUCLEIC ACIDS RESEARCH, **(1999 Jun 1)** 27 (11) 2291-8.
Journal code: 0411011. ISSN: 0305-1048.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AF129267; GENBANK-AF129268; GENBANK-AF129269
EM 199908
ED Entered STN: 19990816
Last Updated on STN: 19990816
Entered Medline: 19990804
AB DNA **methylation** in mammals is required for embryonic development, X chromosome inactivation and imprinting. Previous studies have shown that **methylation** patterns become abnormal in malignant cells and may contribute to tumorigenesis by improper de novo **methylation** and silencing of the promoters for growth-regulatory genes. RNA and protein levels of the DNA methyltransferase DNMT1 have been shown to be elevated in tumors, however murine **stem cells** lacking Dnmt1 are still able to de novo methylate viral DNA. The recent cloning of a new family of DNA methyltransferases (Dnmt3a and Dnmt3b) in mouse which methylate hemimethylated and unmethylated templates with equal efficiencies make them candidates for the long sought de novo methyltransferases. We have investigated the expression of human DNMT1, 3a and 3b and found widespread, coordinate expression of all three transcripts in most normal tissues. Chromosomal mapping placed DNMT3a on chromosome 2p23 and DNMT3b on chromosome 20q11.2. Significant overexpression of DNMT3b was seen in tumors while DNMT1 and DNMT3a were only modestly over-expressed and with lower frequency. Lastly, several novel alternatively spliced forms of DNMT3b, which may have altered enzymatic activity, were found to be expressed in a tissue-specific manner.

=> d 11-20 bib ab

L6 ANSWER 11 OF 189 MEDLINE on STN DUPLICATE 7
AN 2000093982 MEDLINE
DN 20093982 PubMed ID: 10636791
TI DNA **methylation** de novo.
AU Bird A
CS Institute of Cell and Molecular Biology, Edinburgh, UK.. a.bird@ed.ac.uk

SO SCIENCE, **(1999 Dec 17)** 286 (5448) 2287-8.
Journal code: 0404511. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200001
ED Entered STN: 20000124
Last Updated on STN: 20020125
Entered Medline: 20000110

L6 ANSWER 12 OF 189 MEDLINE on STN
AN 1999418719 MEDLINE
DN 99418719 PubMed ID: 10482994
TI Cytosine demethylation of the proteinase-3/myeloblastin primary granule protease gene during phagocyte development.
AU Lubbert M; Tobler A; Daskalakis M
CS Department of Hematology/Oncology, University of Freiburg Medical Center, Germany.
SO LEUKEMIA, **(1999 Sep)** 13 (9) 1420-7.
Journal code: 8704895. ISSN: 0887-6924.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199909
ED Entered STN: 19991012
Last Updated on STN: 20000303
Entered Medline: 19990930
AB Proteinase-3/Myeloblastin (Mbn) is a neutral serine protease and a major constituent of the primary granules of myeloid cells. It can degrade extracellular matrix proteins and has been discussed as a key factor for the initiation of terminal differentiation in promyelocytic cells. Regulation of Mbn closely parallels that of another major primary granule protein, myeloperoxidase (MPO). We examined the expression and DNA **methylation** of Mbn in a model of in vitro differentiation of CD34+ enriched peripheral blood progenitor cells (PBPCs), and in various other myeloid and non-myeloid tissues. Mbn mRNA was undetectable in uncultured PBPCs but was upregulated during their in vitro differentiation. Its expression was enhanced in the presence of G-CSF. Mbn expression was also detected in several myeloid cell lines but not in mature granulocytes, monocytes and macrophages. Partial demethylation at a CpG site within Mbn intron 1 (analyzed by restriction with SmaI) was observed during continued in vitro differentiation of PBPCs. This site was fully demethylated in mature granulocytes, monocytes and macrophages. Variable **methylation** of this site and a second SmaI site located upstream of the putative Mbn promoter region was present in other myeloid and non-myeloid tissues examined.

L6 ANSWER 13 OF 189 MEDLINE on STN DUPLICATE 8
AN 1999423606 MEDLINE
DN 99423606 PubMed ID: 10491537
TI Possible carcinogenic effect of 6-mercaptopurine on bone marrow **stem cells**: relation to thiopurine metabolism.
AU Bo J; Schroder H; Kristinsson J; Madsen B; Szumlanski C; Weinshilboum R; Andersen J B; Schmiegelow K
CS The Laboratory for Pediatric Oncology, The Pediatric Clinic II, The National University Hospital, Copenhagen, Denmark.
NC RO1-GM28157 (NIGMS)
RO1-GM35720 (NIGMS)
SO CANCER, **(1999 Sep 15)** 86 (6) 1080-6.
Journal code: 0374236. ISSN: 0008-543X.
CY United States
DT (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199910
ED Entered STN: 19991014
Last Updated on STN: 20000114
Entered Medline: 19991005
AB BACKGROUND: 6-Mercaptopurine (6MP) has been regarded as nonleukemogenic, even though the cytotoxicity of 6MP depends on the incorporation of 6-thioguanine nucleotides (6TGN) into DNA. In hematopoietic cells this pathway competes with S-**methylation** catalyzed by thiopurine methyltransferase (TPMT). However, methylated 6MP metabolites inhibit purine de novo synthesis and thus may enhance incorporation of 6TGN into DNA. Approximately 10% of white individuals have low TPMT activity as a result of polymorphisms in the TPMT gene. The authors attempted to test the hypothesis that the degree of DNA damage during 6MP therapy might reflect variations in 6MP metabolism and pharmacokinetics. METHODS: The authors measured TPMT activity as well as erythrocyte levels of 6TGN (E-6TGN) and methylated 6MP metabolites (E-MeMP) during 6MP therapy in 439 children with acute lymphoblastic leukemia, 5 of whom later developed secondary myelodysplasia or acute myeloid leukemia (sMDS/AML). RESULTS: The patients who developed sMDS/AML had significantly lower TPMT activity compared with the remaining patients (P = 0.03). The 55 patients with TPMT activity <14 U/mL red blood cells (RBC) (antimode of the bimodal distribution) had a 5-year risk of sMDS/AML of 9 +/- 6% versus 1 +/- 1% for the remaining patients (P = 0.002). Cox regression analysis identified TPMT activity and E-MeMP level as the strongest predictors of risk for sMDS/AML (global P value = 0.02). Patients with low TPMT activity and high E-MeMP levels had the highest risk. All 5 patients with sMDS/AML had E-6TGN and/or E-MeMP levels > the 90% percentiles or had TPMT activity < 14 U/mL RBC. CONCLUSIONS: These data demonstrate an increased leukemogenic risk when 6MP is administered with other cytotoxic agents in patients with low TPMT activity, and indicate that not only high 6TGN levels but also high levels of methylated metabolites may lead to DNA damage.

L6 ANSWER 14 OF 189 MEDLINE on STN
AN 1999280208 MEDLINE
DN 99280208 PubMed ID: 10353741
TI Estrogen receptor **methylation** is associated with improved survival in adult acute myeloid leukemia.
AU Li Q; Kopecky K J; Mohan A; Willman C L; Appelbaum F R; Weick J K; Issa J P
CS The Johns Hopkins Oncology Center, Baltimore, Maryland 21231, USA.
NC 5RO1CA43318 (NCI)
CA12213 (NCI)
CA38926 (NCI)
+
SO CLINICAL CANCER RESEARCH, **(1999 May)** 5 (5) 1077-84.
Journal code: 9502500. ISSN: 1078-0432.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199907
ED Entered STN: 19990816
Last Updated on STN: 19990816
Entered Medline: 19990730
AB Estrogen receptor **methylation** (ERM) is a frequent molecular alteration in adult acute myeloid leukemia (AML). In this study, we sought to determine the clinical characteristics and prognostic significance of ERM in AML. ERM was determined for 268 patients who had

leukemic blasts available for molecular analysis. ERM was measured by Southern blot analysis, and results were obtained for 261 patients (ages 17-69). ERM ranged from 0-99.1%, with a median of 25%. One hundred sixty patients (61%) had ERM values over 15% and were considered ERM+. In a subset of patients analyzed, ERM+ samples had markedly lower ER gene expression compared with ERM- samples. In multiple regression analyses of patient and disease characteristics at diagnosis, two factors had significant independent association with ERM: ERM decreased with increasing age (P = 0.0001) and was significantly lower in patients with French-American-British classification M4 or M5 (P = 0.0019). In regression analyses of outcome measures, ERM had no significant impact on complete remission rate after initial induction therapy. However, ERM+ patients had significantly better overall survival [OS; 18% at 6 years; 95% confidence interval (CI), 12-24% versus 9%; CI, 3-14% for ERM- patients; P = 0.022]. In multiple regression analyses, OS increased with increasing ERM (P = 0.0044). Similar results were seen for relapse-free survival (23% at 6 years; CI, 15-32% for ERM+ versus 10%; CI, 2-19% for ERM-), although the effect of ERM was not statistically significant (P = 0.15 in multiple regression analysis). Our results indicate that ERM at diagnosis may be a favorable prognostic factor for OS in adult AML.

L6 ANSWER 15 OF 189 MEDLINE on STN DUPLICATE 9
AN 2000059230 MEDLINE
DN 20059230 PubMed ID: 10593651
TI Relationship between DNA adduct levels, repair enzyme, and apoptosis as a function of DNA **methylation** by azoxymethane.
AU Hong M Y; Chapkin R S; Wild C P; Morris J S; Wang N; Carroll R J; Turner N D; Lupton J R
CS Faculty of Nutrition, Texas A & M University, College Station 77843-2471, USA.
NC CA 57030 (NCI)
CA 59034 (NCI)
CA 61750 (NCI)
+
SO CELL GROWTH AND DIFFERENTIATION, **(1999 Nov)** 10 (11) 749-58.
Journal code: 9100024. ISSN: 1044-9523.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200001
ED Entered STN: 20000114
Last Updated on STN: 20000114
Entered Medline: 20000103
AB DNA alkylating agent exposure results in the formation of a number of DNA adducts, with O6-methyl-deoxyguanosine (O6-medG) being the major mutagenic and cytotoxic DNA lesion. Critical to the prevention of colon cancer is the removal of O6-medG DNA adducts, either through repair, for example, by O6-alkylguanine-DNA alkyltransferase (ATase) or targeted apoptosis. We report how rat colonocytes respond to administration of azoxymethane (a well-characterized experimental colon carcinogen and DNA-methylating agent) in terms of O6-medG DNA adduct formation and adduct removal by ATase and apoptosis. Our results are: (a) DNA damage is greater in actively proliferating cells than in the differentiated cell compartment; (b) expression of the DNA repair enzyme ATase was not targeted to the proliferating cells or **stem cells** but rather is
confined primarily to the upper portion of the crypt; (c) apoptosis is primarily targeted to the stem cell and proliferative compartments; and (d) the increase in DNA repair enzyme expression over time in the bottom one-third of the crypt corresponds with the decrease in apoptosis in this same crypt region.

L6 ANSWER 16 OF 189 MEDLINE on STN
AN 1999200827 MEDLINE

DN 99200827 PubMed ID: 10102682
TI DNA demethylation during the differentiation of 3T3-L1 cells affects the expression of the mouse GLUT4 gene.
AU Yokomori N; Tawata M; Onaya T
CS Third Department of Internal Medicine, Yamanashi Medical University, Tamaho, Japan.
SO DIABETES, **(1999 Apr)** 48 (4) 685-90.
Journal code: 0372763. ISSN: 0012-1797.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199904
ED Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990415
AB GLUT4 is the major glucose transporter in adipose tissue and skeletal and cardiac muscles. We examined the mechanisms underlying GLUT4 gene expression in 3T3-L1 cells, which express the gene during their differentiation from preadipocytes to adipocytes. In transient transfections, the activity of a mouse GLUT4 promoter extending to -100 bp in the 5'-flanking region did not differ significantly between 3T3-L1 preadipocytes and adipocytes. Promoter activity up to -590 bp in preadipocytes and adipocytes showed a 70% lower and 228% higher activity, respectively, than promoter activity extending to -100 bp. We also examined **methylation** status of the GLUT4 promoter. Up to -100 bp, there were five CpG sites at -11, -30, -58, -63, and -75 bp. Two CpG sites at -11 and -30 bp were highly methylated in preadipocytes (60 and 92%, respectively) and highly demethylated in adipocytes (28.6 and 25%, respectively). Conversely, three CpG sites at -58, -63, and -75 bp were highly demethylated in both preadipocytes and adipocytes (<12%). In gel mobility-shift assays, a fragment extending from -40 to -1 bp generated a **methylation**-sensitive band with nuclear extracts from both preadipocytes and adipocytes when the CpG sites were methylated. Southwestern analysis identified a protein of approximately 55 kDa that bound strongly to the methylated probe. Furthermore, **methylation** of the CpG sites inhibited promoters extending to -50 or -70 bp. These results suggest that in addition to cell type-specific transcription factor, **methylation** of specific CpG sites and the **methylation**-sensitive transcription factor contribute to GLUT4 gene regulation during 3T3-L1 differentiation.

L6 ANSWER 17 OF 189 MEDLINE on STN DUPLICATE 10
AN 1999229671 MEDLINE
DN 99229671 PubMed ID: 10214858
TI Cell lineage specificity in G-CSF receptor gene **methylation**.
AU Felgner J; Heidorn K; Korbacher D; Frahm S O; Parwaresch R
CS Institute of Pathology, German Association of Pathologists, University Kiel, Germany.
SO LEUKEMIA, **(1999 Apr)** 13 (4) 530-4.
Journal code: 8704895. ISSN: 0887-6924.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199905
ED Entered STN: 19990525
Last Updated on STN: 19990525
Entered Medline: 19990510
AB In hematopoiesis the evolution of specialized cell lineages from a common stem cell is mediated by lineage-specific growth factors. The role of DNA **methylation** in the multilevel regulation of the differential gene expression, especially in the case of growth factor receptor genes, has remained elusive. In earlier studies we showed a lineage-specific

methylation pattern of the M-CSF receptor gene c-fms in blood monocytes and tissue macrophages. Here, we provide evidence that a lineage-specific hypomethylation exists for the G-CSF receptor gene for myelomonocytic cells but not in lymphocytes without any interindividual differences. Constant differences were found between alveolar and peritoneal macrophages with a lesser degree of **methylation** in peritoneal macrophages. Acute myelomonocytic leukemias showed an increased **methylation** as compared with normal granulocytes and monocytes. All permanent cell lines analyzed revealed hypermethylation of the G-CSF receptor gene. Lymphocytes of B-CLL showed a strong hypermethylation of this gene. Increased **methylation** has been shown to be inversely correlated with transcriptional gene activities. We conclude that the **methylation** pattern of growth factor receptor genes may be one of the regulatory mechanisms in multi-lineage differentiation.

L6 ANSWER 18 OF 189 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:358194 BIOSIS
DN PREV199900358194
TI Hematopoietic development of primordial germ cell-derived mouse embryonic germ cells in culture.
AU Ohtaka, Takahiko; Matsui, Yasuhisa; Obinata, Masuo [Reprint author]
CS Department of Cell Biology, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryomachi, Aoba-ku, Sendai, 980-8575, Japan
SO Biochemical and Biophysical Research Communications, (July 5, 1999) Vol. 260, No. 2, pp. 475-482. print.
CODEN: BBRCA9. ISSN: 0006-291X.
DT Article
LA English
ED Entered STN: 2 Sep 1999
Last Updated on STN: 2 Sep 1999
AB Induction of hematopoiesis in an embryonic germ (EG) cell line derived from mouse primordial germ cells (PGCs) was examined. When single undifferentiated EG-1 cells were inoculated directly into the methylcellulose medium, both primitive and definitive erythropoiesis were seen in embryoid bodies derived from the EG cells as observed in ES cells, and production of myeloid cell lineages was stimulated by IL-3. These results indicate that EG cells acquired in vitro potency to differentiate toward hematopoietic cells, although they were derived from PGC and are distinct from inner cell mass-derived ES cells with regard to gene expression and patterns of DNA **methylation** corresponding to genomic imprinting. It turns out that they are useful for study of cell differentiation in the animals whose ES cells are not available.

L6 ANSWER 19 OF 189 MEDLINE on STN
AN 1999458301 MEDLINE
DN 99458301 PubMed ID: 10530718
TI Evaluation of clonality in myeloid stem-cell disorders.
AU Gale R E
CS Department of Haematology, University College London, UK.
SO SEMINARS IN HEMATOLOGY, **(1999 Oct)** 36 (4) 361-72. Ref: 86
Journal code: 0404514. ISSN: 0037-1963.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991119
AB Clonality in myeloid stem-cell disorders can be determined using either indirect methods such as analysis of X-chromosome inactivation patterns

(XCIPs), or detection of specific abnormalities such as the chromosomal translocations characteristic of myeloid leukemias. XCIPs are particularly useful for disorders lacking evidence of a specific marker. Most females can be studied using polymerase chain reaction (PCR) analysis of differential DNA **methylation** patterns in the human androgen receptor (HUMARA) or phosphoglycerate kinase (PGK) genes, and approximately 68% can be studied using transcription assays of three polymorphic genes, glucose-6-phosphate dehydrogenase (G6PD), iduronate-2-sulfatase (IDS), and p55. Studies are limited by the incidence of constitutive and acquired (age-related) skewing and results must be carefully interpreted with reference to appropriate control samples. These techniques have been applied to clonality status of hematological disorders, lineage involvement in a clonal process, and detection of clonal evolution.

L6 ANSWER 20 OF 189 MEDLINE on STN DUPLICATE 11
AN 2000021612 MEDLINE
DN 20021612 PubMed ID: 10555141
TI DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo **methylation** and mammalian development.
AU Okano M; Bell D W; Haber D A; Li E
CS Cardiovascular Research Center, Massachusetts General Hospital, Department of Medicine, Harvard Medical School, Charlestown 02129, USA.
NC CA82389 (NCI)
GM52106 (NIGMS)
SO CELL, **(1999 Oct 29)** 99 (3) 247-57.
Journal code: 0413066. ISSN: 0092-8674.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991123
AB The establishment of DNA **methylation** patterns requires de novo **methylation** that occurs predominantly during early development and gametogenesis in mice. Here we demonstrate that two recently identified DNA methyltransferases, Dnmt3a and Dnmt3b, are essential for de novo **methylation** and for mouse development. Inactivation of both genes by gene targeting blocks de novo **methylation** in ES cells and early embryos, but it has no effect on maintenance of imprinted **methylation** patterns. Dnmt3a and Dnmt3b also exhibit nonoverlapping functions in development, with Dnmt3b specifically required for **methylation** of centromeric minor satellite repeats. Mutations of human DNMT3B are found in ICF syndrome, a developmental defect characterized by hypomethylation of pericentromeric repeats. Our results indicate that both Dnmt3a and Dnmt3b function as de novo methyltransferases that play important roles in normal development and disease.

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---Logging off of STN---

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FULL ESTIMATED COST	21.55	21.76

STN INTERNATIONAL LOGOFF AT 13:56:30 ON 17 DEC 2003

WEST Search History

DATE: Wednesday, December 17, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L2	L1 same methylation	16	L2
L1	(restriction landmark genomic scanning) or rlgs	385	L1

END OF SEARCH HISTORY